

ORIGINAL ARTICLE

Aripiprazole does not influence methamphetamine I.V. self-administration in rats

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Abstract

OBJECTIVE: Effects of an atypical antipsychotic and antidepressant aripiprazole on methamphetamine (MET) I.V. self-administration (IVSA) under conditions of behavioural sensitization to MET in rats was investigated in the present study.

METHODS: Adult male Wistar rats were randomly divided into 2 groups: the first group received MET (0.05 mg/kg, intraperitoneally for 14 days); the other received vehicle as a control. During following 14 days of wash-out period the surgery required for IVSA including recovery was realized. The IVSA of MET paradigm was performed in operant chambers under fixed ratio (FR) schedule of reinforcement. When a defined stable intake of MET at FR3 was reached water was given to the animals orally until they achieved stable intake again. Since then aripiprazole (3 mg/kg/day) was administered orally by tube 30 minutes before each self-administration session. For statistic analysis the nonparametric ANOVA Kruskal-Wallis test with Dunn's Multiple Comparisons post test was applied.

RESULTS: A significant decrease of the drug intake was recorded in animals sensitized by MET (MET pretreated) comparing to non-sensitized corresponding group. Aripiprazole did not significantly affect the baseline of MET intake.

CONCLUSION: The behavioural sensitization to MET induced by 14 day intraperitoneal administration of MET decreased the number of the drug doses self-administered per session. This finding might result from increasing efficacy of the drug after sensitization caused by repeated MET intermittent administration. However, aripiprazole did not influence MET intake neither in the behaviourally MET sensitized nor in the non-sensitized rats.

Abbreviations:

MET – methamphetamine; IVSA – IV self-administration

INTRODUCTION

The atypical antipsychotic aripiprazole acts as a partial agonist on dopamine (D2 and D3) receptors. At the same time aripiprazole influences serotonin receptors (agonism at 5-HT1A and antagonism at 5-HT2A receptors). So far it has been approved for therapy of

schizophrenia (so called 3rd generation antipsychotic) (Mailman & Murthy 2010) and manic episodes in bipolar disorder (De Fazio *et al* 2010). Moreover, it has also been studied and recommended for treatment of resistant depressions (Pae *et al* 2011; Pistovcakova & Sulcova 2008) and anxiety disorders (Pae *et al* 2008; Patkar *et al* 2006). As a partial D2/D3 agonist aripiprazole is believed to be able to normalize dopaminergic tone by acting similarly as antagonists during high

dopaminergic firing and as agonists in dopaminergic deficit during withdrawal (Rung *et al* 2008). Due to its mechanism of action aripiprazole seems to be a promising drug in addiction treatment (Backstrom *et al* 2011) as the partial agonism is considered to be useful in treatment of dependence. There is a number of other partial agonists e.g. selective partial nicotine receptor agonist varenicline in nicotine addiction (Vasic *et al* 2011; Walter & Wiesbeck 2009) or partial opioid agonist buprenorphine in substitution therapy of opioid addiction (Frei 2010).

Behavioural sensitization to drugs of abuse and the related adaptations in striatal neurotransmission are thought to play an important role in certain aspects of addiction such as tendency to relaps to drug use in abstaining individuals (Ohmori *et al* 2000). The aim of this study was to utilize the intravenous drug self-administration (IVSA) model, known as a reliable model for testing dependence potential and abuse liability of drugs (Collins *et al* 1984), for quantitative comparison of the methamphetamine (MET) intake of rat males subjected to a repeated drug pretreatment proven (Landa *et al* 2005) to induce behavioural sensitization and drug naïve animals. We expected a decrease of the total number of MET doses self-administered by rats per experimental session based on the increasing response to MET administered due to behavioural sensitization recorded earlier in our laboratory (Kucerova *et al* 2009).

Aripiprazole is able to attenuate locomotor activity induced by behavioural sensitization probably by the antagonistic action on 5-HT_{1A} serotonin receptors (Futamura *et al* 2011). This pharmacological mechanism could be responsible for the decrease of MET intake induced by behavioural sensitization (Kucerova *et al* 2009). Therefore, the rats were treated repeatedly with aripiprazole before IVSA sessions to evaluate its possible impact on spontaneous MET intake.

The working hypotheses on results of aripiprazole effects in the experimental model used were the following: a) decrease of MET intake in non-sensitized rat group due to D₂ partial agonism; b) drug induced suppression of behavioural sensitization in pre-treated (sensitized) animals by normalizing (increasing) MET intake.

MATERIAL AND METHODS

Animals

Adult male albino Wistar rats weighting 180-220 g at the beginning of the study were purchased from Biotest Ltd. (Konarovice, Czech Republic). The animals were housed in groups of five in standardized rat plastic cages. After the catheter implantation surgery was performed, the rats were housed individually. Environmental conditions during the whole study were constant: relative humidity 50-60 %, temperature 23 °C ± 1 °C, inverted 12-hour light-dark cycle (5 a.m. to 5 p.m.

darkness). Food and water were available *ad libitum*. All experiments were conducted in accordance with relevant laws and regulations of animal care and welfare. The experimental protocol was approved by the Animal Care Committee of the Masaryk University Faculty of Medicine, Czech Republic and carried out under the European Community guidelines for the use of experimental animals.

Drugs and treatments

Methamphetamine from Sigma Chemical, Co., St Louis, MO, USA was used for both initial drug pretreatment and the IVSA model. The administration of MET prior to IVSA was according to the following dosing regimen, which was successfully used in previous studies carried out at our laboratory (Kucerova *et al* 2006; Landa *et al* 2005, 2008) to induce behavioural sensitization: 0.5 mg/kg/day, intraperitoneally, for 14 days, administered in home cages. The identical volume and route of administration of saline solution (SAL) was used for all control treatments. MET dose available in the operant cage for IVSA was 0.08 mg per infusion with the maximum number of infusions obtainable in one session set to 50 which was a procedure producing reinforcing effects in the same model of IVSA in our laboratory (Vinklerova *et al* 2002).

Aripiprazole was used in a dissolved tablet form (ABILIFY 15 mg oral tablets, Bristol-Meyers Squibb S.r.L., Anagni, Italy) at the dose of 3 mg/kg/day administered orally by tube 45 minutes before the self-administration session.

I.V. self-administration surgery and procedures

Under the general anaesthesia with ketamine 50 mg/kg and xylazine 8 mg/kg given intraperitoneally (NARKAMON 5% and ROMETAR 2%, Bioveta a.s., Czech Republic, in combination with isoflurane inhalation for induction to anaesthesia) a permanent intracardiac silastic catheter was implanted through the external jugular vein to the right atrium. The outer part of the catheter exited the skin in the midscapular area. A small nylon bolt was fixed on the skull with dental acrylic to stainless-steel screws embedded in the skull; this served as a tether to prevent the catheter from being pulled out while the rat was in the self-administration chamber. The catheters were flushed daily before all the sessions with 0.2 ml of heparinized cephalosporine (VULMIZOLIN 1.0 inj sicc, Biotika a.s., Slovak Republic) solution (0.05 mg/kg in saline with 2.5 I.U./kg) and 0.05 ml of heparin (HEPARIN LECIVA inj. sol. 1x10ml/50 I.U., Zentiva a.s., Czech Republic) solution (5 I.U.) to prevent infection and occlusion of the catheter. During this procedure the blood was aspirated daily to assess the patency of the catheter, and changes in general behaviour, weight and other circumstances were recorded. When a catheter was found blocked the animal was excluded from the analysis.

IV self-administration protocol

Standard experimental cages with two nose-poke holes allocated on one side of the cage were programmed by software L2T2 (Coulbourn Instruments, USA) and the IVSA sessions were conducted under the fixed ratio (FR) schedule of reinforcement starting at FR1 (each correct response reinforced). Fixed-ratio requirements were raised (e.g. FR2 - two correct responses required, etc.); when the animal fulfilled the following conditions for three consecutive sessions:

- at least 70% preference of the drug-active nose-poke;
- minimum intake of 10 infusions per session;
- stable intake of the drug (maximum 10 % deviation) in three consecutive sessions.

Active nose-pokes led to the activation of the infusion pump and administration of a single infusion followed by 30 sec time-out, while the other nose-pokes were recorded but not rewarded. The cage was illuminated by a house light which was twinkling when administering infusion and off in the time-out. The daily IVSA sessions lasted 90 minutes and took place regularly between 7 a.m. and 4 p.m. during the dark period of the inverted light cycle.

After reaching stable baseline intake each animal was subjected to water administration (control) orally by tube 45 minutes before the self-administration session and the possible effect on the MET intake was recorded. When the rat developed stable MET intake on oral water administration, it was replaced by aripiprazole solution (3 mg/kg/day) administered by the same manner as water before.

Experimental groups

There were 14 rats at the beginning of the experiment. However, due to complicated surgical procedures 1 of the subjects was lost.

The final groups as introduced to the first IVSA session follow:

- SAL group (n=7): 14 days of saline (SAL) intraperitoneal pretreatment, the experiment was completed by 7 animals
- MET group (n=7): 14 days of MET (0.5 mg/kg/day) intraperitoneal pretreatment, the experiment was completed by 6 animals

Statistical Data analysis

The means of MET intake were compared when the animals reached a stable intake of MET at FR2 and FR3 protocol. For statistical analysis of differences in MET IVSA the nonparametric ANOVA - Kruskal-Wallis test with Dunn's Multiple Comparisons post test - was used. Level of statistical significance was determined to $p < 0.05$.

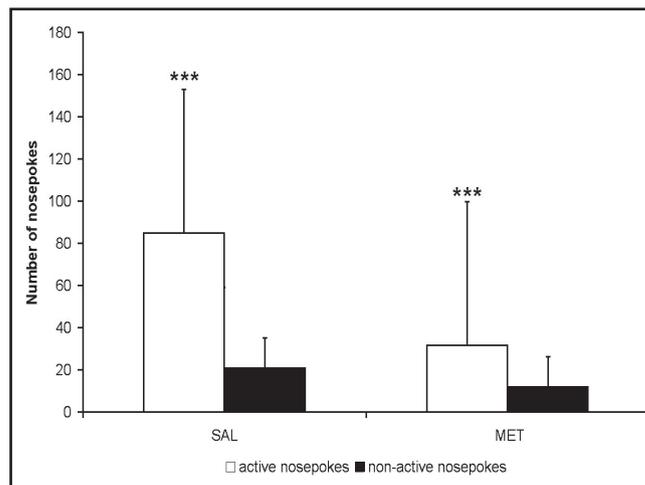


Figure 1: Graph displays mean (\pm SEM) numbers of nosepokes during baseline intake. Both, methamphetamine (MET) and saline solution (SAL) pretreated rats performed significantly higher number of the nosepokes associated with methamphetamine ($p < 0.001$).

RESULTS

The **Figure 1** shows that both groups of rats, pretreated with saline or MET, demonstrated significant ($p < 0.001$) prevalence of active nosepokes, i.e. those associated with MET reward.

Spontaneous intake of MET defined as a mean number of infusions significantly differed between groups. Chronic intermittent MET pretreatment led to decrease of MET intake in the IVSA model as expected due to behavioural sensitization (**Figure 2**). This effect was statistically significant in comparison to non-treated baseline intake ($p < 0.001$) as well as in comparison to intake during oral water pretreatment administration ($p < 0.05$).

Figure 3 exhibits the effect of aripiprazole oral administration on the MET intake in IVSA. The significant difference between experimental groups induced by behavioural sensitization was abolished by aripiprazole administration. There was no significant effect of oral pretreatment with water/aripiprazole on MET intake in neither previously drug naïve group (SAL) nor behaviourally sensitized group (MET).

DISCUSSION

According to results of our earlier studies in the same paradigm (Kucerova *et al* 2009) in the present study the significantly higher responding to nose pokes associated with drug administration in all animals tested confirmed the rewarding effect of methamphetamine as expected.

This study correlates with our previous findings that Wistar male rats repeatedly pre-treated with MET ("MET" group) self-administer significantly lower

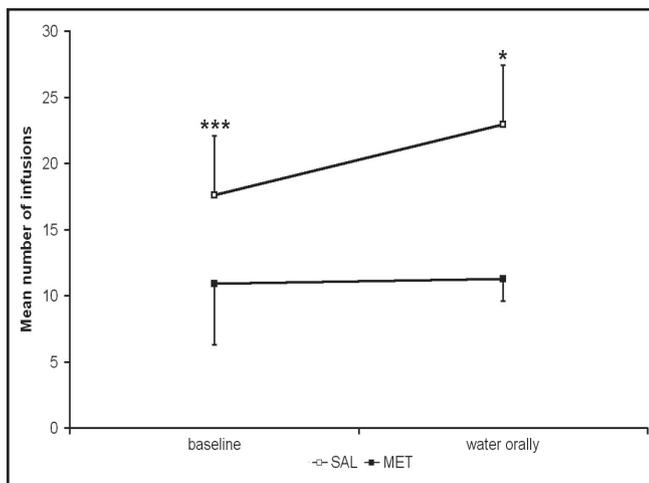


Figure 2: Graph displays mean (\pm SEM) numbers of MET infusions self-administered by the animals after reaching stable baseline intake and influence of water pretreatment 45 minutes before session orally. There is a statistically significant difference between the sensitized (MET group) and non-sensitized (SAL group) experimental groups in the baseline MET intake ($p < 0.001$) as well as in stable intake with control oral water administration before the session ($p < 0.05$). However, there was not recorded any significant alteration of MET intake induced by oral administration procedure (water).

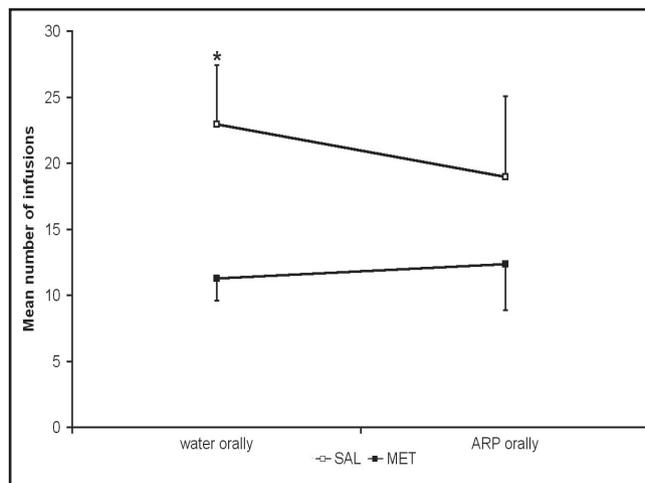


Figure 3: Graph displays influence of aripiprazole pretreatment on the mean (\pm SEM) numbers of MET infusions self-administered by the animals when stable intake was reached. There is apparent significant difference between the experimental groups at conditions of oral water administration ($p < 0.05$). When aripiprazole (3 mg/kg/day) was administered 45 minutes before the session orally, there was neither statistically significant difference between the experimental groups anymore nor significant alteration of MET intake in each group.

number of MET infusions under a fixed ratio schedule compared to animals pretreated with saline (“SAL” group) (Kucerova *et al* 2009). Higher MET rewarding effects decreased drug-seeking behavioural signs in previously sensitized animals what can be considered as behavioural sensitization in this model. At the dose which did not influence rat locomotor activities in the open field test (Pistovcakova & Sulcova 2008) aripiprazole did not elicit any influence on the MET intake in drug naïve nor in sensitized rats. The observed significant difference in drug intake between experimental groups induced by behavioural sensitization was abolished by aripiprazole treatment. However, this cannot be interpreted as a suppression of behavioural sensitization, because MET intake was not significantly increased in sensitized animals by aripiprazole administration.

Clinically, aripiprazole was examined for possible attenuation of drug intake in MET addict volunteers, where it seemed to increase rewarding effects of MET. However, the main limitation of this study was a small sample size (8 in each arm) and authors themselves recognize a low probability of aripiprazole potential to increase MET rewarding effects (Newton *et al* 2008). Clinical studies with alcohol addicts show inconsistent results but in some cases they demonstrate ability of aripiprazole to reduce chronic alcohol consumption in co-administration (Vergne & Anton 2010).

In the preclinical study by Mavrikaki *et al* 2010 a completely opposite result was shown as aripiprazole attenuated rewarding effects of amphetamine in the intracranial self-stimulation model and hyperlocomotion

paradigm induced by amphetamine. This result was recorded after acute drug administration as well as after chronic intermittent treatment leading to behavioural sensitization to amphetamine which indicates the possible intensified firing in the dopaminergic reward pathway (Mavrikaki *et al* 2010). However, in IV self-administration paradigm 3 mg/kg dose aripiprazole (equal dose as in our experiment) was recorded to decrease intake of d-amphetamine. This suggests an attenuation of reinforcing effects of d-amphetamine in Wistar rats (identical strain as in our experiment). The opposite effect was recorded in the same paradigm when aripiprazole increased d-amphetamine intake at the dose of 1 mg/kg (Backstrom *et al* 2011). In preclinical experimental paradigm of relapse to drug of abuse intake, aripiprazole exhibited capacity to reduce cocaine relapse rate in two different rat strains (Feltenstein *et al* 2007; Roman & Gyertyan 2009).

Present experiments did not confirm the efficacy of aripiprazole in management of MET intake in the rat model of IVSA of methamphetamine. Nevertheless, the literature available refers a certain potential of aripiprazole in treatment of psychostimulant addiction such as amphetamine, MET or cocaine dependency. Summarizing the currently available data on aripiprazole, we can speculate that aripiprazole might be useful in reduction of the relapse rate in addicted individuals, rather than influencing the overall MET intake. Efficacy of aripiprazole seems to be largely influenced by the choice of appropriate (probably rather high) dose and the treatment paradigm itself. Thus, despite of the contradictory data obtained, it is too early to discard

aripiprazole from suggested indication. Further studies are needed to evaluate its benefit in treating drug addiction.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial interest in this manuscript and no affiliations (relationships) to disclose.

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